Appendix 3

sTable 1- Summary of findings: Sodium alginate in preterm infants

Sodium alginate compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: Sodium alginate **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes assessed with: Combined pH and impedance monitoring (follow-up: range 6h to 24h)	In two studies Sodium alginate significantly decreased the number of acid GOR episodes but did not influence the number of non-acid GOR episodes. In one study Total GOR Episodes: RR 0.59 (0.53 to 0.65) (95% CI). In the other study, sodium alginate significantly decreased the number of GOR (DG vs. DF: median 49 vs. 58.5) [a,b,c]	60 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]
A reduction in reflux symptoms (apnoea related to GOR) assessed with: Combined multichannel intraluminal impedance and pH monitoring and polysomnography (follow-up: 6h)	The frequency of apnoeas related to GOR did not differ between DG and DF meals (median [range] 0 [0–0.67] vs. 0 [0–0.47]). Total Apnoea Episodes: RR 1.06 (0.96 to 1.18) (95% CI) [a,b]	28 (1 RCT)	⨁⨁◯◯ LOW [d,e]
Adverse events assessed with: Not specified (follow-up: range 6h to 24h)	No adverse event was recorded during the study period.	60 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	None of the included studies examined the effect of sodium alginates on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. DG: drug given

b. DF: drug free

c. GOR: gastroesophageal reflux

d. Evidence downgraded by 1 point (-1) for risk of selection bias.

e. Evidence downgraded by 1 point (-1) for indirectness as only a single study contributed data, and evidence was therefore based on a single patient population.

sTable 2 - Summary of findings: Proton pump inhibitors in preterm infants

Proton pump inhibitors compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: Proton pump inhibitors **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes assessed with: Twenty-four-hour esophageal pH monitoring (reflux index score)	Omeprazole therapy (10 participants; 1 study) significantly reduced gastric acidity, oesophageal acid exposure and the number and duration of acid reflux episodes compared to placebo. There was no statistically significant difference between the esomeprazole and placebo groups in the percentage of change from baseline after 14 days of treatment in the total number of GORD-related signs and symptoms (52 participants; 1 study).	62 (2 RCTs)	⨁⨁◯◯ LOW [a,b]
A reduction in reflux symptoms assessed with: Bedside symptom charts (vomit/regurgitations, choking/coughing, bradycardia attributed to GOR, behavioural/crying, feeding difficulties, irritability or pain, recurrent postprandial apnoeas and oxygen desaturation within two hours postprandial period)	Despite the normalization of acid reflux in most patients, the number of symptomatic events of vomiting, apnea, bradycardia or behavioral changes was not significantly changed by omeprazole (10 participants; 1 study). One study (162 participants) detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GORD. No significant differences were observed between the esomeprazole and placebo groups (52 participants; 1 study) in the percentage of change from baseline to the end of treatment in the total number of gastrointestinal, neurobehavioral or cardiorespiratory events.	224 (3 RCTs)	⨁⨁◯◯ LOW [a,b,c]
Adverse events	Treatment-emergent serious AEs (SAEs), particularly lower respiratory tract infections, were significantly more frequent in the lansoprazole group compared with the placebo group (10 vs 2; P.032). Overall, few adverse events (AEs) were reported, and the number of patients with AEs was similar between the esomeprazole and placebo groups. The most commonly reported AE was decrease in oxygen saturation (52 participants; 1 study). No SAEs were reported in the esomeprazole-treated patients and 4 SAEs (neonatal bradycardia, cyanosis, inappropriate device signal detection, and infantile apneic attack) were reported in 3 placebo patients. Omeprazole therapy (10 participants; 1 study) was not associated with the occurrence of any serious adverse events.	224 (3 RCTs)	⨁⨁◯◯ LOW [a,b,c]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	None of the included studies examined the effect of proton pump inhibitors on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(0 studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

sTable 3 - Summary of findings: H2 receptor antagonists in preterm infants

H2 receptor antagonists compared to Placebo for gastroesophageal reflux in preterm infants

Patient or population: preterm infants **Intervention**: H2 receptor antagonists **Comparison**: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
A reduction in reflux episodes	The included study did not examined the effect of H2 receptor antagonists on the reduction of reflux episodes.	(0 studies)	-
A reduction in reflux symptoms (Bradycardia) assessed with: Telemetry and nursing documentation	No evidence of efficacy was found for Ranitidine to reduce bradycardia. The mean number of bradycardia episodes per day in the combined drug periods was 4.6 (SD = 3.1), and the mean number of episodes per day in the combined placebo periods was 3.6 (SD = 2.7) There was a statistically significant difference, with fewer episodes during the placebo periods. The mean difference (drug minus placebo) was 0.94 episodes per day, with a P value of 0.04.	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Adverse events assessed with: Clinical assessment	There were no adverse effects attributed to ranitidine. However, it may have increased, bradycardia episodes in preterm infants with bradycardia attributed to GOR.	17 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Time taken to establish full enteral feeds, length of hospital stay, necrotising enterocolitis, suspected or proven sepsis	No studies examined the effect of H2 receptor antagonists on the incidence of necrotising enterocolitis, suspected or proven sepsis, time taken to establish full enteral feeds and length of hospital stay.	(0 studies)	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect